

Statistical Analysis Plan

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Revision History

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Statistical Analysis Organization Signature Page

Study Title: A Single-Center Clinical Study to Evaluate the Efficacy and Safety of Allogeneic Natural Killer (NK) Cell Therapy for Corneal Ulcers with Stromal Infiltration

Clinical Trial Protocol: Refer to the Study Protocol for details

Eye Hospital of Shandong First Medical University

2026/06/10

(Shandong Eye Hospital)



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1. Introduction

This Statistical Analysis Plan (SAP) has been developed for the study entitled “A Single-Center Clinical Study to Evaluate the Efficacy and Safety of Allogeneic Natural Killer (NK) Cell Therapy for Corneal Ulcers with Stromal Infiltration” and specifies the statistical analysis methods, data handling principles, and presentation of study results.

2. Study Objectives and Endpoints

2.1 Study Objectives

Primary Objective: To evaluate the safety of allogeneic NK cell transplantation

Secondary Objective: To evaluate its efficacy and conduct an exploratory analysis

2.2 Endpoints

2.2.1 Efficacy Endpoints

1 Primary Efficacy Endpoint: Central corneal thickness after cell transplantation.

2 Secondary Efficacy Endpoints:

1. Best-corrected visual acuity after cell transplantation;
2. Corneal endothelial cell density after cell transplantation;
3. Corneal clarity recovery after cell transplantation;
4. Incidence of adverse events after cell transplantation.

3. Study Design

3.1 Overall Study Design

This is a single-center clinical study designed to preliminarily evaluate the efficacy and safety of allogeneic NK Cell transplantation in the treatment of Mooren's ulcer. The study population consisted of 6 patients aged 18 to 85 years who met specific diagnostic criteria for Mooren's ulcer. The intervention was conducted from May 2026 to November 2027. Eligible participants must provide written informed consent and meet the corresponding inclusion and exclusion criteria. The primary evaluation indicators include corneal epithelial integrity, central corneal thickness (CCT), recovery of corneal transparency, corneal endothelial cell density and morphology, and best-corrected visual acuity (BCVA) at each follow-up visit post-transplantation.

3.2 Study Methods

On the scheduled day of transplantation (defined as Day 0), subjects will receive allogeneic NK cell transplantation. The cells are administered via conjunctival fornix injection using a 30-gauge needle at varying doses: low-dose group (1×10^6 cells in 500 μL), medium-dose group (3×10^6 cells in 500 μL), and high-dose group (6×10^6 cells in 500 μL).

At Day 5 ± 2 post-transplantation, slit-lamp biomicroscopy, tonometry, optical coherence tomography (OCT), and B-scan ultrasonography will be performed to assess for any significant ocular complications. Should such complications occur, the principal investigator and relevant physicians will manage them promptly based on clinical judgment. Subjects will be discharged once deemed clinically stable and no longer requiring hospitalization.

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4. Statistical Analysis Methods

4.1 Statistical Analysis Software

All statistical analyses will be performed using statistical analysis software such as GraphPad Prism and SPSS.

4.2 Analysis of General Data

Descriptive statistical analysis was performed in this study. Measurement data were expressed as mean $\pm$ standard deviation (SD) or median (interquartile range, IQR). Categorical data were presented as number (percentage). Intra-group comparisons before and after treatment were performed using the paired t-test or Wilcoxon signed-rank test according to the data distribution. All statistical tests were two-sided, and a P-value < 0.05 was considered statistically significant.

4.3 Handling of Missing and Outlier Data

Unless otherwise specified, no imputation will be performed for missing data.

Handling of Missing AE Dates or Missing Assessment of Relationship to Study Method

a) Missing AE Start Date

If the year and month are known and precede the year and month of the first cell transplantation, the AE start date will be imputed as the last day of the known month.

If the year and month are known and are the same as the year and month of the first cell transplantation, the AE start date will be set as the date of the first cell transplantation.

If the year and month are known and follow the year and month of the first cell transplantation, the AE start date will be imputed as the first day of the known month.

If only the year is known and the year precedes the year of the first cell transplantation, the AE start date will be imputed as December 31 of that year.

If only the year is known and the year is the same as the year of the first cell transplantation, the AE start date will be set as the date of the first cell transplantation.

If only the year is known and the year follows the year of the first cell transplantation, the AE start date will be imputed as January 1 of that year.

If the year, month, and day are all missing, the date of the first cell transplantation will be used as the AE start date. If the imputed start date occurs after the AE end date, the AE end date will be used as the start date.

b) Missing AE End Date

If the year and month are known, the AE end date will be imputed as the last day of the known month.

If only the year is known, the AE end date will be imputed as December 31 of that year.

In all other cases, the AE end date will be considered missing.

c) Missing Assessment of Relationship to Study Drug

If the assessment of the relationship between an AE and the study procedure is missing, the AE will be summarized as a study-related adverse event.

4.4 Definitions

4.4.1 Study Design: Cell Injection

4.4.2 Reference Start Date

Unless otherwise specified, the reference start date is defined as the date of first transplantation initiation.

4.4.3 Study Day

Study Day is defined as the number of days between the date of a specific event or assessment (e.g., AE onset date, date of examination completion, visit date) and the reference start date. The calculation is performed as follows:

- 1 If the event date occurs on or after the reference start date

Study Day = Event date (e.g., visit date, event onset date, assessment date) – Reference start date + 1

- 2 If the event date occurs before the reference start date:

Study Day = Event date (e.g., visit date, event onset date, assessment date) – Reference start date

Study Day will be presented in the data listings. If the event begins prior to the reference start date, the Study Day will be displayed as a negative value.

4.4.4 Baseline

Baseline value is defined as the last valid measurement (scheduled/unscheduled) before cell injection. If the time precision cannot be distinguished, the baseline value is defined as the last valid measurement from a scheduled visit before cell injection.

4.4.5 Definition of Study Periods

The overall study consists of three main periods: the screening period, the transplantation period, and the observation period.

4.5 Analysis Populations

Screened Set (SCN): All subjects who have signed the informed consent form.

Randomized Set (RND): All subjects who have been assigned a randomization code.

Full Analysis Set (FAS): All randomized subjects who have received at least one surgical procedure.

Per Protocol Set (PPS): All randomized subjects who have received the surgical procedure, completed treatment, and had no major protocol deviations.

Safety Set (SS): All subjects who have received at least one surgical procedure.

5 Subject Disposition

5.1 Subject Distribution

The conduct of the clinical trial and the status of the analysis populations will be described with respect to the following aspects:

- Number of subjects screened
- Number of screening failures
- Number and percentage of subjects who completed the clinical trial
- Number and percentage of subjects who discontinued the trial prematurely, categorized by reason

5.2 Protocol Deviations

Protocol deviations for all subjects will be summarized by type and severity of deviation, and presented as counts and percentages for each group and overall.

6. Demographic and Other Baseline Characteristics

6.1 Demographic Characteristics

The summary of demographic characteristics will include the following:

- Age (years)

- Sex (male/female)
- Ethnicity (Han Chinese/Other)

6.2 Baseline Characteristics

6.2.1 Medical History, Surgical History, and Other Relevant History

Medical history, surgical history, and other relevant history will be summarized using counts and percentages.

7 Efficacy Analysis

7.1 Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint of this clinical trial is the change from baseline in corneal thickness after cell transplantation. Descriptive statistical analysis will be performed for the primary efficacy endpoint.

7.2 Analysis of the Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

1. Best-corrected visual acuity after cell transplantation;
2. Corneal endothelial cell density after cell transplantation;
3. Recovery of corneal clarity after cell transplantation;
4. Incidence of adverse events after cell transplantation.

Descriptive statistical analyses will be performed for all secondary efficacy endpoints.

8 Safety Analysis

8.1 Adverse Events (AE)

An adverse event (Adverse Event, AE) is defined as any unfavorable and unintended medical occurrence in a subject who has received the cell therapy, which may present as signs, symptoms, diseases, or abnormal laboratory findings, and does not necessarily have a causal relationship with the cell therapy.

In this study, the relationship between AEs and the cell therapy will be categorized into five levels: definitely related, probably related, possibly related, possibly unrelated, and definitely unrelated. AEs assessed as definitely related, probably related, or possibly related will be summarized as treatment-related adverse events.

A serious adverse event (Serious Adverse Event, SAE) is defined as any adverse medical event that results in death, is life-threatening, results in permanent or severe disability or loss of

function, requires inpatient hospitalization or prolongation of existing hospitalization, or results in a congenital anomaly or birth defect.

8.2 Laboratory Tests

8.3 Other Safety Data

8.3.1 Vital Signs

8.3.2 12-Lead Electrocardiogram (ECG)

8.4 Ophthalmic Examinations

9 Deviations Between the Statistical Analysis Plan and the Clinical Trial Protocol

None